CERIANNA- fluoroestradiol f 18 injection
Zionexa US Corporation

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CERIANNA™ safely and effectively. See full prescribing information for CERIANNA.

CERIANNA™ (Fluoroestradiol F 18) injection, for intravenous use
Initial U.S. Approval: 2020

INDICATIONS AND USAGE

CERIANNA is a radioactive diagnostic agent indicated for positron emission tomography (PET) imaging. Fluoroestradiol F 18 is indicated for characterization of estrogen receptor status of known or suspected metastatic lesions in patients with confirmed ER-positive breast cancer. (1)

DOSAGE AND ADMINISTRATION

- Recommended dose is 222 MBq (6 mCi), with a range of 111 MBq to 222 MBq (3 mCi to 6 mCi), administered as an intravenous injection over 1 to 2 minutes. (2.2)
- Recommended imaging start time is 80 minutes (range 20 minutes to 80 minutes) after drug administration. (2.4)
- The recommended dose for an adult weighing 70 Kg is 222 MBq with an allowable range from 111 to 222 MBq (3 – 6 mCi). This activity injected can be adapted to the body weight of the patient, the type of camera used and the acquisition mode.
- See full prescribing information for additional preparation, administration, imaging, and radiation dosimetry information. (2)

DOSAGE FORMS AND STRENGTHS

Injection: 148 MBq/mL to 3,700 MBq/mL (4 mCi/mL to 100 mCi/mL) of fluoroestradiol F 18 in a multiple-dose vial. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

• Risk of Misdiagnosis. Do not use CERIANNA in lieu of biopsy when biopsy is indicated in patients with recurrent or metastatic breast cancer. Pathology or clinical characteristics that suggest a patient may benefit from systemic hormone therapy should take precedence over a discordant negative CERIANNA scan. (5.1)
• Radiation Risks. Ensure safe drug handling and patient preparation procedures to protect patients and health care providers from unintentional radiation exposure. (2.1, 2.3, 5.2)

ADVERSE REACTIONS

Reported adverse reactions include: injection-site pain and dysgeusia
To report SUSPECTED ADVERSE REACTIONS, contact Zionexa US Corp at +1.844.946.6392 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. (6)

DRUG INTERACTIONS

Drugs such as tamoxifen and fulvestrant that block the estrogen receptor reduce the uptake of fluoroestradiol F 18. Do not delay indicated therapy in order to administer CERIANNA. Image patients with CERIANNA prior to starting systemic endocrine therapies that block ER. (2.3, 7.1)

USE IN SPECIFIC POPULATIONS

• Lactation: Interrupt breastfeeding. Advise a lactating woman to avoid breastfeeding for 4 hours after CERIANNA administration. (8.2)
See 17 for PATIENT COUNSELING INFORMATION.

Revised: 5/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

CERIANNA is indicated for use with positron emission tomography (PET imaging) for characterization of estrogen receptor (ER) status of known or suspected metastatic lesions in patients with confirmed ER-positive breast cancer.

Limitations of Use

Tissue biopsy should be used to confirm recurrence of breast cancer and to verify ER status by pathology. CERIANNA is not useful for imaigng other receptors, such as human epidermal growth factor receptor 2 (HER2) and the progesterone receptor (PR)

2 DOSAGE AND ADMINISTRATION

2.1 Radiation Safety - Drug Handling

CERIANNA is a radioactive drug. Only authorized persons qualified by training and experience should receive, use, and administer CERIANNA. Handle CERIANNA with appropriate safety measures to minimize radiation exposure during administration [see Warnings and Precautions (5.2)]. Use waterproof gloves and effective radiation shielding, including syringe shields, when preparing and handling CERIANNA.

2.2 Recommended Dose and Administration Instructions

Recommended Dosage
The recommended amount of radioactivity to be administered for PET imaging is 222 MBq (6 mCi), with a range of 111 MBq to 222 MBq (3 mCi to 6 mCi), administered as a single intravenous injection of 10 mL or less over 1 to 2 minutes.

Preparation and Administration
• For patient preparation instructions, see (2.3).
• Use aseptic technique and radiation shielding when withdrawing and administering CERIANNA.
• Visually inspect the radiopharmaceutical solution. Do not use if it contains particulate matter or if it is cloudy or discolored (CERIANNA is a clear, colorless solution).
• CERIANNA may be diluted with 0.9% Sodium Chloride Injection, USP.
• Assay the dose in a suitable dose calibrator prior to administration.

Post-Administration Instructions
• Follow the CERIANNA injection with an intravenous flush of 0.9% Sodium Chloride injection, USP.
• Dispose of any unused CERIANNA in compliance with applicable regulations

2.3 Patient Preparation

Assessment for Drug Interactions
Image patients with CERIANNA prior to starting systemic endocrine therapies that target ER (e.g., ER modulators and ER down-regulators) [see Drug Interactions (7.1)].

Patient Hydration and Voiding
Instruct patients to drink water to ensure adequate hydration prior to administration of CERIANNA and to continue drinking and voiding frequently during the first hours following administration to reduce radiation exposure.

Pregnancy Status
Assessment of pregnancy status is recommended in females of reproductive potential before administering CERIANNA.

2.4 Image Acquisition

Position the patient supine with arms above the head, if possible. The recommended start time for image acquisition is 80 minutes after the intravenous administration of CERIANNA. Scan duration adapted from the range of 20 minutes to 30 minutes and imaging start times adapted within the range of 20 minutes to 80 minutes may be customized according to the equipment used and patient and tumor characteristics for optimal image quality.

2.5 Image Interpretation

Uptake of fluoroestradiol F 18 depends on ER density and function in tumors and physiologic tissue, including in liver, ovary, and uterus. Detection of ER-positive tumors should be based on comparison with tissue background outside of organs with high physiologic uptake and regions with high activity due to hepatobiliary and urinary excretion.

2.6 Radiation Dosimetry

Radiation absorbed dose estimates are shown in Table 1 for organs and tissues of adults from

intravenous administration of CERIANNA. The radiation effective dose resulting from administration of 222 MBq (6 mCi) of CERIANNA to an adult weighing 70 kg is estimated to be 4.9 mSv. Critical organs include the liver, gallbladder, and uterus. When PET/CT is performed, exposure to radiation will increase by an amount dependent on the settings used for the CT acquisition.

Table 1 Estimated Radiation Absorbed Doses in Various Organs/Tissues in Adults who Received FLUOROESTRADIOL F 18

Organ	**Mean Absorbed Dose per unit of Activity Administered (mGy/MBq)**
Adrenals	0.023
Brain	0.01
Breasts	0.009
Gallbladder	0.102
Lower large intestine	0.012
Small Intestine	0.027
Stomach	0.014
Upper large intestine	0.03
Heart wall	0.026
Kidney	0.035
Liver	0.126
Lungs	0.017
Muscle	0.021
Ovaries	0.018
Pancreas	0.023
Red Marrow	0.013
Bone surface	0.014
Skin	0.005
Spleen	0.015
Testes	0.012
Thymus	0.014
Thyroid	0.012
Urinary bladder	0.05
Uterus	0.039
Lens	0.009
Effective dose equivalent = 0.022 mSv/MBq	

3 DOSAGE FORMS AND STRENGTHS

Injection: clear, colorless solution in a multiple-dose vial containing 148 MBq/mL to 3,700 MBq/mL (4 mCi/mL to 100 mCi/mL) of fluoroestradiol F 18 at end of synthesis.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Misdiagnosis

Inadequate Tumor Characterization and Other ER-Positive Pathology
Breast cancer may be heterogeneous within patients and across time. CERIANNA images ER and is not useful for imaging other receptors such as HER2 and PR. The uptake of fluoroestradiol F 18 is not specific for breast cancer and may occur in a variety of ER-positive tumors that arise outside of the breast, including from the uterus and ovaries. Do not use CERIANNA in lieu of biopsy when biopsy is indicated in patients with recurrent or metastatic breast cancer.

False Negative CERIANNA Scan
A negative CERIANNA scan does not rule out ER-positive breast cancer [see Clinical Studies (14)]. Pathology or clinical characteristics that suggest a patient may benefit from systemic hormone therapy should take precedence over a discordant negative CERIANNA scan

5.2 Radiation Risks

Diagnostic radiopharmaceuticals, including CERIANNA, expose patients to radiation [see Dosage and Administration (2.6)]. Radiation exposure is associated with a dose-dependent increased risk of cancer. Ensure safe drug handling and patient preparation procedures to protect patients and health care providers from unintentional radiation exposure [see Dosage and Administration (2.1) and (2.3)].

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of CERIANNA was evaluated from published clinical studies of 1207 patients with breast cancer receiving at least one fluoroestradiol F 18 administration. The following adverse reactions occurred at a rate < 1%:
• General disorders: injection-site pain
• Neurological and gastrointestinal disorders: dysgeusia

7 DRUG INTERACTION

7.1 Systemic Endocrine Therapies that Target Estrogen Receptors

Certain classes of systemic endocrine therapies, including ER modulators and ER down-regulators, block ER, reduce the uptake of fluoroestradiol F 18, and may reduce detection of ER-positive lesions after administration of CERIANNA. Drugs from these classes such as tamoxifen and fulvestrant may block ER for up to 8 and 28 weeks, respectively. Do not delay indicated therapy in order to administer CERIANNA. Administer CERIANNA prior to starting systemic endocrine therapies that block ER [see Dosage and Administration (2.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk SummaryAll radiopharmaceuticals, including CERIANNA, have the potential to cause fetal harm

depending on the fetal stage of development and the magnitude of radiation dose. Advise a pregnant woman of the potential risks of fetal exposure to radiation from administration of CERIANNA.

There are no available data on CERIANNA use in pregnant women. No animal reproduction studies using fluoroestradiol F 18 have been conducted to evaluate its effect on female reproduction and embryo-fetal development.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defects, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation

Risk Summary

There are no data on the presence of fluoroestradiol F 18 in human milk, or its effects on the breastfed infant or milk production. Lactation studies have not been conducted in animals. Advise a lactating woman to avoid breastfeeding for 4 hours after CERIANNA administration in order to minimize radiation exposure to a breastfed infant.

8.4 Pediatric Use

The safety and effectiveness of CERIANNA in pediatric patients have not been established.

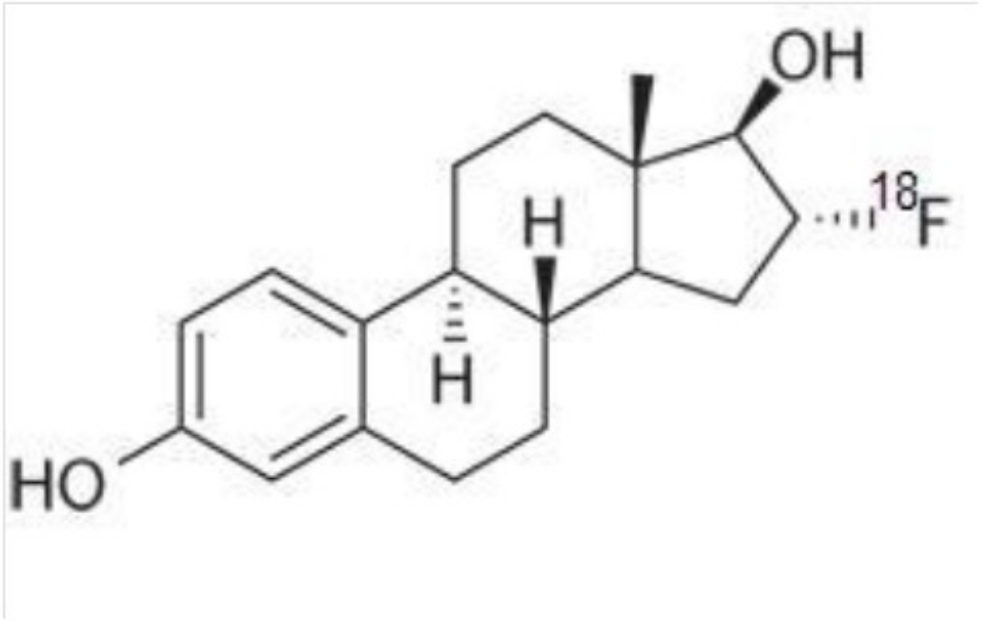
8.5 Geriatric Use

Clinical studies of fluoroestradiol F 18 injection did not reveal any difference in pharmacokinetics or biodistribution in patients aged 65 and over.

11 DESCRIPTION

11.1 Chemical Characteristics

CERIANNA contains fluoroestradiol fluorine 18 (F 18), a synthetic estrogen analog. Chemically, fluoroestradiol F 18 is [18F]16α-fluoro-3,17β-diol-estratriene-1,3,5(10). The molecular weight is 289.37, and the structural formula is:



CERIANNA is a sterile, clear, colorless solution for intravenous injection, with an osmolarity of 340 mOsm. Its pH ranges between 4.5 to 7.0. The composition of the final product in 40 mL solution is

fluoroestradiol no more than 5 µg, fluoroestradiol F 18 148 MBq/mL to 3,700 MBq/mL (4 mCi/mL to 100 mCi/mL), sodium ascorbate 0.44% w/v in sodium chloride 0.9% w/v, and ethanol no more than 3.2% w/v..

11.2 Physical Characteristics

CERIANNA is radiolabeled with F 18, a cyclotron produced radionuclide that decays by positron emission to stable oxygen 18 with a half-life of 109.8 minutes. The principal photons useful for diagnostic imaging are the coincident pair of 511 keV gamma photons, resulting from the interaction of the emitted positron with an electron (Table 2).

Table 2 Principal Radiation Produced from Decay of Fluorine 18 Radiation

Energy	(keV)	% Abundance
Positron	249.8	96.7
Gamma	511	193.5

11.3 External Radiation

The point source air-kerma coefficient for F 18 is 3.75 x 10^{-17} Gy m^2/(Bq s). The first half-value thickness of lead (Pb) for F 18 gamma rays is approximately 6 mm. The relative reduction of radiation emitted by F 18 that results from various thicknesses of lead shielding is shown in Table 3. The use of 8 cm of Pb will decrease the radiation transmission (i.e., exposure) by a factor of about 10,000.

Table 3 Radiation Attenuation of 511 keV Gamma Rays by Lead Shielding

Shield Thickness cm of Lead (Pb)	Coefficient of Attenuation
0.6	0.5
2	0.1
4	0.01
6	0.001
8	0.0001

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of action

Fluoroestradiol F 18 binds ER. The following binding affinity: Kd = 0.13 ± 0.02 nM, Bmax = 1901 ± 89 fmol/mg, and IC50 = 0.085 nM, was determined in an ER-positive human breast cancer cell line (MCF-7).

12.2 Pharmacodynamics

The relationship between fluoroestradiol F18 plasma concentrations and image interpretation has not been studied. Fluoroestradiol F18 uptake measured by PET in human tumors is directly proportional to tumor ER expression measured by in vitro assays.

12.3 Pharmacokinetics

Distribution

After intravenous injection, 95% of fluoroestradiol F 18 is bound to plasma proteins. Fluoroestradiol F

18 distributes primarily to hepatobiliary system, and also to small and large intestines, heart wall, blood, kidney, uterus and bladder.

Metabolism
Fluoroestradiol F 18 is metabolized in the liver. At 20 minutes after injection, approximately 20% of circulating radioactivity in the plasma is in the form of non-metabolized fluoroestradiol F 18. At 2 hours after injection, circulating fluoroestradiol F 18 levels are less than 5% of peak concentration.

Excretion
Elimination is by biliary and urinary excretion.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
No long-term studies in animals were performed to evaluate the carcinogenic potential of CERIANNA.

Mutagenesis
Fluoroestradiol was evaluated by in vitro bacterial reverse mutation assay (Ames test) and in vitro L5178Y/TK+/- mouse lymphoma mutagenesis assay. Fluoroestradiol was negative for genotoxicity by Ames test at up to 1.25 µg per plate for 5 tester strains (Salmonella typhimurium tester strains TA98, TA100, TA1535 and TA1537 and Escherichia Coli tester strain WP2 uvrA) in the presence or absence of S9 metabolic activation. Fluoroestradiol was negative for genotoxicity by L5178Y/TK+/- mouse lymphoma mutagenesis assay at up to 8 ng/mL in the absence or presence of S9 metabolic activation.

Potential in vivo genotoxicity of fluoroestradiol was evaluated in a rat micronucleus assay. In this assay, fluoroestradiol did not increase the number of micronucleated polychromatic erythrocytes (MN-PCEs) at 51 µg/kg/day, when given for 14 consecutive days. However, CERIANNA has the potential to be mutagenic because of the F 18 radioisotope.

Impairment of Fertility
No studies in animals have been performed to evaluate potential impairment of fertility in males or females.

14 CLINICAL STUDIES

The effectiveness of CERIANNA for detecting ER-positive non-primary breast cancer lesions was evaluated based on published study reports of fluoroestradiol F 18. Study 1 (NCT01986569) enrolled 90 women (median age 55 years, 39% premenopausal) with histologically confirmed invasive breast cancer. The patients had first known or suspected recurrence of treated breast cancer or stage IV metastatic breast cancer. Recent biopsy of lesions outside of bone and areas with high physiologic fluoroestradiol F 18 uptake was also required [see Dosage and Administration (2.5)]. Patients concurrently using estrogen receptor modulators or fulvestrant discontinued them 60 days prior to fluoroestradiol F 18 administration. Concurrent use of aromatase inhibitors was permitted. Three image readers were blinded to all clinical information, except for the location of the largest biopsied lesion, for which pathologists independently provided an Allred score (0 to 8). The image readers scored the intensity of FES uptake on a three-point scale relative to normal biodistribution as either “decreased,” “equivocal,” or “increased” (1 to 3).

Image reader performance for distinguishing between ER-positive and ER-negative fluoroestradiol F 18 uptake was compared to biopsy in 85 patients. Of the 47 patients with positive biopsy (Allred score ≥ 3), 36 were positive on imaging (majority reader score = 3). Ten of 11 patients with false negative imaging had Allred scores between 3 and 6 [see Warnings and Precautions (5.1)]. Of the 38 patients with negative biopsy, all 38 were negative on imaging.

Study 2 (NCT00602043) in 13 patients showed similar results.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

CERIANNA is supplied in a 50 mL multiple-dose glass vial (NDC# 72874-001-01) containing a clear, colorless injection solution at a strength of 148 MBq/mL to 3,700 MBq/mL (4 mCi/mL to 100 mCi/mL) fluoroestradiol F 18 at the end of synthesis. Each vial contains multiple doses and is enclosed in a shield container to minimize external radiation exposure.

16.2 Storage and Handling

Storage
Store CERIANNA at controlled room temperature (USP) 20°C to 25°C (68°F to 77°F). Store CERIANNA upright in the original container with radiation shielding. The expiration date and time are provided on the container label. Use CERIANNA within 10 hours from the time of the end of synthesis.

Handling
This preparation is approved for use by persons under license by the Nuclear Regulatory Commission or the relevant regulatory authority of an Agreement State.

17 PATIENT COUNSELING INFORMATION

Radiation Risks
Advise patients of the radiation risks of CERIANNA [see Warnings and Precautions (5.2)]. Instruct patients to drink water to ensure adequate hydration prior to administration of CERIANNA and to continue drinking and voiding frequently during the first hours following administration to reduce radiation exposure [see Dosage and Administration (2.3)].

Pregnancy
Advise a pregnant woman of the potential risks of fetal exposure to radiation doses with CERIANNA [see Use in Specific Populations (8.1)].

Lactation
Advise a lactating woman to avoid breastfeeding for 4 hours after CERIANNA administration in order to minimize radiation exposure to a breastfed infant [see Use in Specific Populations (8.2)].

Distributed by:

ZIONEXA US CORP.
205 East 42nd Street
New York, NY 10017

PRINCIPAL DISPLAY PANEL

Multiple Dose Vial

CERIANNA™ (Fluoroestradiol F 18) Injection
148 MBq/mL to 3,700 MBq/mL (4 mCi/mL to 100 mCi/mL) @ End of Synthesis
For Intravenous Use Only

Date of manufacture:	Lot#
Expiration date & time:_____; _____hr:min Volume: _____ mL Store at 20°C to 25°C (68°F to 77°F) Store upright in a shielded container Do not use if cloudy or if it contains particulate matter	Contains: 148 MBq/mL to 3,700 MBq/mL (4 mCi/mL to 100 mCi/mL) of no-carrier added Fluoroestradiol F 18 @ EOS*; sodium ascorbate 0.44% w/v in sodium chloride 0.9% w/v and ethanol no more than 3.2% w/v
Usual dosage: See prescribing information	
CAUTION: RADIOACTIVE MATERIAL	Distributed by: Zionexa US Corp, New York, NY 10017 **Rx ONLY**

Lead Shield (canister) Label

NDC 72874-001-01 Multiple Dose Vial

CERIANNA™(Fluoroestradiol F 18) Injection
148 MBq/mL to 3,700 MBq/mL (4 mCi/mL to 100 mCi/mL) @EOS*
For Intravenous Use Only

Sterile, Non-pyrogenic
Date/time of calibration: _____; _____hr:min
Expiration date & time:_____; _____hr:min
Volume: _____ mL

Contains: 148 MBq/mL to 3,700 MBq/mL (4 mCi/mL to 100 mCi/mL) of no-carrier added Fluoroestradiol F 18 @ EOS*; sodium ascorbate 0.44% w/v in sodium chloride 0.9% w/v and ethanol no more than 3.2% w/v

Usual dosage: See prescribing information

Do not use if cloudy or if it contains particulate matter
*EOS = End of Synthesis

Diagnostic
Lot# _____
Concentration: _____mCi/mL at time of calibration
Total Activity: _____mCi at time of calibration

(Expires 10 hours after EOS*)

Store at 20°C to 25°C (68°F to 77°F)
Store upright in a shielded container
Aseptically withdraw and handle doses

[18F] Half-Life = 109.7 minutes
Calculate correct dosage from date and time of calibration

CAUTION: RADIOACTIVE MATERIAL

Distributed by: Zionexa US Corp
New York, NY 10017

Rx ONLY

CERIANNA

fluoroestradiol f 18 injection

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:72874-001
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**

FLUOROESTRADIOL F-18 (UNII: T32277KB09) (FLUOROESTRADIOL F-18 - UNII:T32277KB09)	FLUOROESTRADIOL F-18	100 mCi in 1 mL

Inactive Ingredients	
Ingredient Name	**Strength**
SODIUM ASCORBATE (UNII: S033EH8359)	
SODIUM CHLORIDE (UNII: 451W47IQ8X)	
ALCOHOL (UNII: 3K9958V90M)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:72874-001-01	50 mL in 1 VIAL, MULTI-DOSE; Type 0: Not a Combination Product	05/20/2020	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA212155	05/20/2020	

Labeler - Zionexa US Corporation (081116818)

Establishment

Name	Address	ID/FEI	Business Operations
Kreitchman PET Center		010861487	positron emission tomography drug production(72874-001)

Revised: 5/2020 Zionexa US Corporation